SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:

Cardiac CryoAblation System

Device Trade Names:

Arctic Front® Cardiac CryoAblation Catheter (Models 2AF232 and 2AF282)

Freezor® *MAX* Cardiac CryoAblation Catheter (Models 239F3 and 239F5)

CryoConsole (Model 106A2)

Manual Retraction Kit (Model 20MRK)

Applicant's Name and Address:

Medtronic CryoCath LP

16771 Chemin Ste Marie

Kirkland, Quebec, CANADA, H9H 5H3

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100010

Date of FDA Notice of Approval: December 17, 2010

Expedited: Not Applicable

II. INDICATIONS FOR USE

The Arctic Front® Cardiac CryoAblation Catheter and CryoConsole (Arctic Front® Cryocatheter System) are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

The Freezor® *MAX* Cardiac CryoAblation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with Arctic Front® Cryocatheter for the following uses:

- gap cryoablation to complete electrical isolation of the pulmonary veins,
- cryoablation of focal trigger sites, and
- creation of ablation line between the inferior vena cava and the tricuspid valve.

III. CONTRAINDICATIONS

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Use of the Arctic Front® Cardiac CryoAblation Catheter is contraindicated as follows:

- in the ventricle because of the danger of catheter entrapment in the chordae tendinae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

Use of the Freezor® *MAX* Cardiac CryoAblation Catheter is contraindicated in patients with the following conditions:

- active systemic infections
- cryoglobulinemia
- other conditions where the manipulation of the catheter would be unsafe (for example, intracardiac mural thrombus)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Arctic Front® Cardiac CryoAblation Catheter, Freezor® *MAX* Cardiac CryoAblation Catheter, and CryoConsole labeling.

V. DEVICE DESCRIPTION

The Arctic Front® Cardiac CryoAblation Catheter and CryoConsole (Arctic Front® Cryocatheter System) consists of:

- The Arctic Front® Cryocatheter (23 mm and 28 mm diameters) is a deflectable, over-the-wire balloon catheter used to ablate cardiac tissue for the purpose of isolating pulmonary veins in the treatment of drug refractory symptomatic paroxysmal AF. It is used together with the FlexCath® Steerable Sheath, as well as the CryoConsole and related components.

- The CryoConsole is used in performing cardiac ablation procedures. During a procedure, pressurized liquid N_2O (nitrous oxide) refrigerant is injected from a tank in the CryoConsole. The refrigerant travels through an ultra-fine injection tube which passes through the coaxial umbilical cable and the catheter shaft to the cryoablation balloon. The balloon is under vacuum pressure causing the nitrous oxide gas to be returned to the CryoConsole and evacuated into the hospital suction or evacuation system.

- Accessory devices (coaxial umbilical, electrical umbilical, auto-connection box, ECG cable and footswitch), all of which are PMA-approved (P020045).

- The Manual Retraction Kit is also an accessory device designed for use with Arctic Front® Cryocatheters and provides an alternative means of inflating and deflating the balloon catheter, in the unlikely case that the normal methods of inflating and deflating

the balloon are unsuccessful. The manual retraction kit is a sterile device intended for single use.

The **Freezor *MAX* Cardiac CryoAblation Catheter** is a flexible, steerable catheter used to ablate cardiac tissue. It is used together with the CryoConsole and related components for performing focal endocardial cryoablation as an adjunctive device in the treatment of paroxysmal atrial fibrillation in conjunction with the Arctic Front® Cryocatheter. The tip of the Freezor *MAX* Cryocatheter reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter, freezing the adjacent tissue.

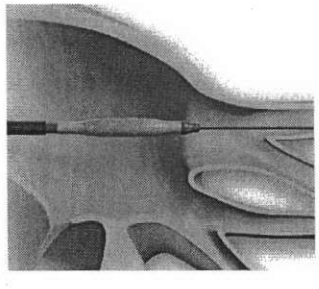
The devices listed in the table below with the specified trade names, catalog numbers, and primary distinguishing features are the subject of the PMA application.

Device Trade Names	Catalog Numbers	Features
Arctic Front® Cardiac CryoAblation Catheter	2AF232	23 mm balloon diameter
	2AF282	28 mm balloon diameter
Freezor® *MAX* Cardiac CryoAblation Catheter	239F3 (medium)	Blue curve (55mm reach)
	239F5 (long)	Orange curve (66 mm reach)
CryoConsole	106A2	
Manual Retraction Kit	20MRK	

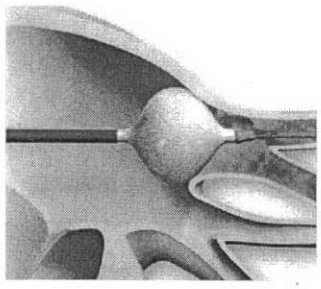
The **Flex**The **FlexCath® Steerable Sheath**, which has been cleared for marketing under K081049, is used to deliver Arctic Front® Cryocatheters to the pulmonary vein ostia. The FlexCath® Steerable Sheath is a percutaneous catheter introducer fitted with a hemostasis valve to allow for introduction, withdrawal and swapping of catheters and wires while preventing air ingress and minimizing blood loss.

The principles of operation of the Arctic Front® Cryocatheter System are described below:

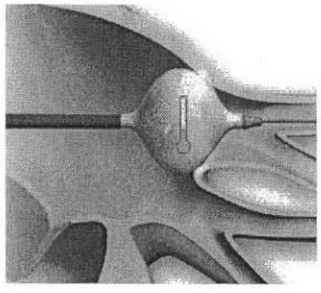
Once the FlexCath® Steerable Sheath has been introduced into the left atrium via a transseptal puncture, the Arctic Front® Cryocatheter is passed through the FlexCath® lumen over a guidewire and into the left atrium in an uninflated state. Typically the guidewire has already been placed in the target pulmonary vein.



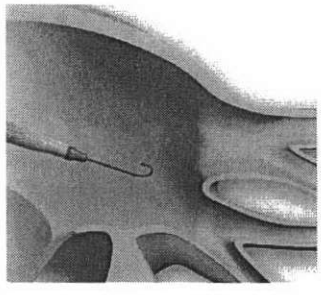
The Arctic Front® Cryocatheter is inflated in the atrium and gently positioned at the ostium of the target pulmonary vein. Balloon position and the extent of venous occlusion are verified by injection of contrast or the use of intracardiac ultrasound.



When occlusion has been achieved, cryoablation is initiated. Refrigerant is automatically injected into the inflated balloon, removing heat and causing the balloon temperature to drop to cryoablation levels. The tissue freezes at the point of contact with the balloon, resulting in cell death and conduction block.



After the cryoablation cycle is complete, the flow of refrigerant is stopped and the Arctic Front® Cryocatheter balloon warms to body temperature. The balloon is then deflated and withdrawn into the left atrium, where the procedure can be repeated in the same or another pulmonary vein.



If subsequent testing reveals gaps in the ablation line, additional balloon cryoablations can be performed, or the Freezor® *MAX* Cryocatheter can be used for focal touch-ups. Freezor *MAX* Cryocatheter can also be used to ablate other arrhythmogenic foci as needed.

Please refer to the Arctic Front® Cardiac CryoAblation Catheter and Freezor® *MAX* Cardiac CryoAblation Catheter Technical Manuals, or the CryoConsole Operator's Manual for further details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of symptomatic paroxysmal atrial fibrillation, including the following:

- Commercially available PMA-approved devices
- Pharmacological therapy for rate and/or rhythm control
- Electrical or pharmacologic cardioversion
- Surgical intervention to create atrial lesions

- Implantable devices to control heart rates

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Arctic Front® Cardiac CryoAblation Catheter is marketed in the following countries: European Union, Switzerland, Turkey, Australia, Hong Kong, and Qatar.

The Freezor® *MAX* Cardiac CryoAblation Catheter is marketed for treatment of cardiac arrhythmias in the following countries: European Union, Canada, Australia, China, Argentina, Israel, and South Korea. The Freezor® *MAX* Catheter is PMA-approved in the United States as a surgical device for minimally invasive cardiac surgery procedures, including surgical treatment of cardiac arrhythmias.

The CryoConsole is marketed in the following countries: European Union, Switzerland, Turkey, Canada, Australia, Hong Kong, Israel, and Qatar.

The Manual Retraction Kit is marketed in the following countries: European Union, Australia, and Canada.

There are no countries from which the Arctic Front® Cardiac CryoAblation Catheter, Freezor® *MAX* Cardiac CryoAblation Catheter, CryoConsole or Manual Retraction Kit have been withdrawn from marketing for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of the device:

- Anemia
- Anxiety
- Atrial flutter
- Back pain
- Bleeding from puncture sites
- Blurred vision
- Bradycardia
- Bronchitis
- Bruising
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Nerve injury

- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Cough
- Death
- Diarrhea
- Dizziness
- Esophageal damage
- Pericardial effusion
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Tachycardia
- Transient ischemic attack
- Urinary infection
- Vasovagal reaction
- Visual changes

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

Pre-clinical testing of the Arctic Front® Cardiac CryoAblation Catheter and CryoConsole included verification and validation testing (device level, system level, and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies. Performance testing was conducted to demonstrate design integrity. All tests performed which were identified in standards or guidance documents were based on the product specification requirements. In the tests described below, the Arctic Front® Cardiac CryoAblation Catheter and CryoConsole were manufactured by trained manufacturing operators. "Pass" as used below denotes that the devices and system met established product specifications and/ or performance criteria, or were in conformance with the requirements of the standards tested to. Testing results confirmed that the Arctic Front® Cardiac CryoAblation Catheter and CryoConsole met the product specifications.

A. Laboratory Studies

Table 1 below summarizes the bench testing for the Arctic Front® Cryocatheter including reliability, mechanical and electrical integrity, and performance test results.

Table 1: Arctic Front® Cryocatheter Bench Testing

Test	N	Acceptance criteria	Result
Catheter Diameter and Balloon Profile	9	Successful insertion and withdrawal through 12F sheaths: FlexCath and 12F Cook (Mullins)	Pass
Tensile Strength	21	≥ 3.4 lbs	Pass
Flexibility and Kink Test			
Buckling Force	6	Buckling force less than Freezor *MAX* Cryocatheter	Pass
Stiffness	6	At least as flexible as the Freezor *MAX* Cryocatheter	Pass
Kink Resistance	6	None (Comparison to prior design with higher likelihood of kinking for bend angles of 90°)	No catheter exhibited any kinking for bend angles up to 270°
Torque Strength			
Torque Response	10	Torque response should exist (with no required value)	Catheter has a 1:0.6 torque response
Torque to failure	10	No mechanical catheter damage for one full torque of handle with a fixed tip (360°)	Pass
Balloon Tests			
Balloon fatigue (Repeat balloon inflation)	21	None Any unexpected behaviour (related to balloon and catheter preparation) will be assessed in terms of criticality through a Failure Mode Analysis	Pass
Balloon Preparation			
Balloon Deflatability Test			
Catheter Radiopacity	2	None Comparison between Arctic Front Cryocatheters with polyimide and Nitinol injection tubes	Catheter with the nitinol injection tube is less visible on fluoroscopy
Minimum Balloon Burst Strength	19	Test to quantify the burst pressure of the Arctic Front Cryocatheter and to derive an acceptance criterion to qualify inner balloon lots arriving at incoming inspection	Incoming inspection criterion for inner balloon: the minimum 99.9% lower bound for inner burst pressure should be ≥ the 99.9% upper bound of the worst case fault condition.

Table 1: Arctic Front® Cryocatheter Bench Testing

Test	N	Acceptance criteria	Result
Catheter Body Burst Pressure	19	Test to quantify the burst pressure of the Arctic Front Cryocatheter and to derive an acceptance criterion to qualify outer balloon lots arriving at incoming inspection	Incoming inspection criterion for the outer balloon: the minimum 95% lower bound for outer burst pressure should be ≥ the 95% upper bound of the outer balloon pressure response to an inner burst.
Contrast Media Flow Rate	12	Contrast flow rate ≥ that of the Arctic Circler Balloon catheter (previous design)	Pass
Deflection Pattern (and Trackability)	8	None Comparison to Arctic Circler CurvilLinear catheter deflection pattern	Similar deflection pattern until approximately 90° of deflection
Deflection Fatigue	15	Fifty (50) deflections in each direction without failure or shaft deformation	Pass
Flexion Fatigue	8	≥ 3.3 lbs	Pass
Balloon Surface Temperature	12	Arctic Front Cryocatheter in an in-vitro model shall be ≥ -41.0°C (STD=10.7)	Pass
Leak and Blood Detection Verification	16	None Quantitative assessment of the response time for the leak and blood detection system	A pre-injection delay time of 30 seconds was recommended

N: number of units tested

Table 2 below summarizes the bench testing for the CryoConsole.

Table 2: CryoConsole Bench Testing

Test	Sample Size	Acceptance Criteria	Results
Electrical Safety / Electromagnetic Compatibility	1	UL 60601-1 CAN/CSA-C22.2 601-1 M90 CAN/CSA-C22.2 601.1 1S1-94 CAN/CSA-C22.2 601.1 B-98 ANSI C63.18-1997 EN 60601-2	Pass
ESD Radiated RF Immunity Fast transient bursts Harmonic current emissions Surge immunity Voltage fluctuation Immunity to disturbances Power frequency magnetic field	1	EN 61000-4-2: EN 61000-4-3 EN 61000-4-6 EN 61000-4-4 EN 61000-3-2 EN 61000-4-5 EN 61000-3-3 & EN 61000-4-11 EN 61000-4-6 EN 61000-4-8	Pass
EMC Immunity Testing	1	UL 60601-1	Pass
Radiated Emissions Limits Test	1	FCC 47 CFR Part 15 subpart B ICES-003	Pass
CSA Certification	1	CAN/CSA-C22.2 601-1 M90 CAN/CSA-C22.2 601.1 1S1-94 CAN/CSA-C22.2 601.1 B-98 UL 60601-1	Pass
System Verification Testing	4	Acceptance criteria as per finished product documentation	Console was verified to meet design inputs in line with Product Requirements
System Validation Testing	4	Console to pass acceptance criteria as per finished product documentation	Console was validated as per protocol

Biocompatibility Testing

Biocompatibility testing of the Arctic Front® Cryocatheter was conducted in accordance with the ISO 10993 standard and FDA/CDRH/ODE Blue Book Memorandum G95-1, "Use of International Standard ISO-10993". Based on ISO-10993, the catheter is an externally communicating device, which contacts circulating blood for "limited" duration (less than 24 hours). A summary of the results are reported in Table 3: Biocompatibility Testing Summary below and demonstrate that the Arctic Front® Cryocatheter is biocompatible as per ISO 10993.

Table 3: Biocompatibility Testing Summary

Test	Result
Cytotoxicity Using the ISO Elution Method	Pass
Murine Local Lymph Node Assay	Pass
ISO Intracutaneous Study (Extract)	Pass
USP and ISO Systemic Toxicity (Extract)	Pass
USP Pyrogen Study (Material-Mediated Pyrogenicity)	Pass
In Vitro Hemolysis Study (Modified ASTM-Extraction Method)	Pass
Plasma Recalcification Time Coagulation Study	Pass
In-Vivo Thromboresistance Study	Pass
C3a Complement Activation Assay	Pass
SC5b-9 Complement Activation Assay	Pass

Patient contacting materials of the Arctic Front catheter tested for biocompatibility are listed in Table 4 below:

Table 4: Patient Contacting Material Tested for Biocompatibility

Catheter Component	Material	Color
Balloon	90A Urethane	natural
Balloon Adhesive	Dymax 204	natural
Catheter Tip	Pebax 3533 (loaded with 20% $BaSO_4$)	Pantone 3015C
Multi-Durometer Shaft	Pebax 5533 (no loading) Pebax 2533 (loaded with 20% $BaSO_4$) Pebax 5533 (loaded with 20% $BaSO_4$)	Pantone 3015C
Inner Guide Wire Lumen Surface	Polytetrafluoroethylene (Teflon-coating)	natural

B. Animal Studies

Medtronic CryoCath LP conducted a series of studies involving over 150 animals on several iterations of its cryoablation devices to demonstrate the safety and performance of using cryoenergy to ablate pulmonary vein and atrial tissue. The studies encompassed an evaluation of focal and non-balloon catheters, early balloon catheter designs, and the initial and commercial designs of Arctic Front® Cryocatheter evaluated in the STOP AF Pivotal Trial and the CAP-AF Continued Access Study, respectively.

The Arctic Front® Cryocatheter studies demonstrated the utility of the FlexCath® Steerable Sheath to facilitate positioning of the balloon at the pulmonary vein (PV)-atrial junction and the ability of the Arctic Front® Cryocatheter and CryoConsole to safely create acute and chronic electro-anatomical disconnection of the PVs from the atrium. A final animal study was performed to confirm the equivalent safety, performance, and handling characteristics of the commercial design of Arctic Front® Cryocatheter evaluated in the CAP-AF Continued Access Study with the initial design studied in the STOP AF Pivotal Trial.

The safety and performance of the Arctic Front cryocatheter was evaluated in several animal studies. The Arctic Front® Cryocatheter studies demonstrated the utility of the FlexCath® Steerable Sheath to facilitate positioning of the balloon at the pulmonary vein (PV)-atrial

junction and the ability of the Arctic Front® Cryocatheter and CryoConsole to safely create acute and chronic electro-anatomical disconnection of the PVs from the atrium.

The Arctic Front CryoAblation catheters were tested to confirm the short and long-term safety and effectiveness of pulmonary vein CryoAblation. Study objectives included assessment of the degree of electrical and histopathological isolation, structural changes in the pulmonary veins, and the extent of thrombus formation or other potential damage to cardiac and surrounding structures (PCP-123B, PCP-139).

A comparison study of initial (IDE clinical study) and final (device to be commercialized) design of Arctic Front catheter was performed in 9 canines with a 7 day survival. Equivalence in temperature performance, handling characteristics, and histopathological response was demonstrated (PCP-149).

In addition two (2) training sessions for physicians were performed (PCP-136) to prepare investigators to participate in European clinical trial, and (PCP-141) for the pivotal IDE STOP AF PS-023 clinical trial.

Device	Study ID	No. of Animals	Species/ Survival	Summary of Investigation	Results
Arctic Front (first design)	PCP-123B	14	Canine/ Acute 3-months	Determination of acute and chronic safety and efficacy of the Arctic Front system	- Acutely, 69% PVs were isolated with 4 minute ablations - At 3 months, 63% remained chronically isolated - No damage to adjacent structures was noted - Complete tissue-balloon contact predicts success - Use of FlexCath sheath facilitated ablation
Arctic Front (first design)	PCP-136	1	Canine/ Acute	Physician in-vivo training with Arctic Front system.	- Training was successful - No safety issues were reported
Arctic Front (first design)	PCP-139	21	Canine/ Acute and 3-month	Histopathological and temperature study of esophageal, phrenic nerve and pulmonary vein tissue	- Cryolesions can extend up to 4.5 mm from the balloon surface - No significant esophageal damage was reported - Loss of phrenic nerve conduction can be created by cryoablation with subsequent recovery - The Arctic Front system was effective in isolating pulmonary veins - No significant PV narrowing was not observed
Arctic Front (first design)	PCP-141	12	Canine/ Acute	Physician in-vivo training with Arctic Front system.	- Training was successful - No safety issues were reported

Device	Study ID	No. of Animals	Species/ Survival	Summary of Investigation	Results
Arctic Front (first & final design)	PCP-149	9	Canine 7 days	Study system performance equivalence of 2AF230 (IDE device) and 2AF231/232 (device to be commercialized) catheters and system	- Demonstration of equivalent temperature performance between first and final design of AF catheter - Physician feedback confirmed the equivalence of handling - Demonstration of equivalent histopathological response

C. Additional Studies

Sterilization, Packaging and Shelf Life

The Arctic Front® Cryocatheter is supplied as a sterile, single use medical device, ready for use. The Arctic Front Cryocatheter® is secured in a tray (to protect the catheter from damage), then the tray is covered by a lid (to prevent movement during transport), which are then placed in a sealed pouch. The pouched catheters are inserted in a carton box. The packaged catheters are then exposed to a 2X ethylene oxide (EtO) sterilization process. Routine validation is performed in accordance with ANSI/AAMI/ISO11135-1: 2007 and ANSI/AAMI/ISO109993-7:2008.

Bioburden is monitored according to Medtronic CryoCath's internal procedure to ensure appropriate sterility assurance level (SAL) of the finished products. To control the bioburden, the catheters are manufactured in a Class 100,000 controlled area. The bioburden is assessed prior to sterilization and was determined by a contract laboratory.

The packaging utilized to maintain integrity of the sterile barrier is a Biax Nylon with Polyethylene / Tyvek pouch. Thirty (30) packaged catheters were exposed to 2X EtO sterilization and simulated shipping and distribution (including manual handling, vehicle stacking, loose load vibration, low pressure high altitude testing and vehicle vibration) and the integrity of the pouches and seals were verified per ASTM 2096-04 *Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)* and ASTM F88-07a *Standard Test Method for Seal Strength of Flexible Barrier Material.* Arctic Front® Cryocatheter performance and packaging integrity met the acceptance criteria of the distribution stimulation tests.

The Arctic Front® Cryocatheter is labeled with a 6 month shelf life.

X. SUMMARY OF CLINICAL STUDY

The applicant performed two clinical studies [STOP AF Pivotal Trial (PS-023) and CAP AF Continued Access Protocol (PS-024)] to establish a reasonable assurance of safety and effectiveness of ablation with the Arctic Front® Cardiac CryoAblation Catheter System for the treatment of patients with symptomatic paroxysmal atrial fibrillation (PAF) in the US and

Canada under IDE # G031059. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
Feasibility: CryoSTOP AF (PS – 012)	Non-randomized, multicenter, feasibility study	Provide an initial evaluation of the Arctic Circler® Balloon and Arctic Front® Cardiac CryoAblation Systems in patients with PAF	4 (US)	Enrolled: 39 Treated: 33 (15 Arctic Circler balloon, 18 Arctic Front)
Pivotal: STOP AF (PS – 023)	Prospective, multi-center, randomized, controlled clinical trial	Demonstrate safe and effective use of the investigational devices when used to treat PAF	26 (23 US, 3 Canada)	Enrolled: 304 Randomized: 245 (163 Cryo, 82 AAD)
Continued Access: CAP AF (PS – 024)	Non-randomized multi-center study	Designed to provide continued access to the investigational devices as well as provide acute scientific evidence regarding the safety and effectiveness of the modified investigational devices	8 (US)	Enrolled: 69 Treated to date (study ongoing): 65

A. Study Design

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation. Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone or sotalol) (Amiodarone was not considered a study AF drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

At the time of protocol development there were no approved catheter ablation devices approved for the treatment of paroxysmal atrial fibrillation. The use of an anti-arrhythmic drug control arm was implemented for comparison in the STOP AF clinical trial to assess the safety and effectiveness of the Arctic Front Cardiac Cryoablation System. It was not until the STOP AF protocol was nearly completed and all subjects were enrolled and treated that FDA approved the first RF catheter for the treatment of PAF, so changes to the study design and potential changes to the control group were not contemplated. Minor changes were made to the protocol over the course of the clinical trial; however, there were no changes that impacted the overall approach or designed intent of the STOP AF study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the STOP AF study was limited to patients who met the following inclusion and exclusion criteria:

Inclusion:	Exclusion:
Documented PAF: • diagnosis of paroxysmal atrial fibrillation (PAF) AND • 2 or more episodes of AF during the 2 months preceding the Start Date, at least 1 of which must be documented with a tracing	Any previous left atrial (LA) ablation (except permissible retreatment subjects)
≥ 18 and ≤ 75 years of age	Any previous LA surgery
Documented failure of one or more (≥ 1) Primary AF Drugs (1° AFDs) for effectiveness.	Anteroposterior LA diameter > 5.0 cm by TTE during the 3 month interval preceding the Consent Date
Clinically eligible to follow the Standard Antiarrhythmic Treatment procedure for both groups, control or experimental.	Presence of any cardiac valve prosthesis
Willing to comply with: • Atrial Fibrillation Drug (AFD) treatment regardless of randomization • TTM procedures for full 12 month follow-up period	Clinically significant mitral valve regurgitation or stenosis
	Any treatment with amiodarone during the 3 month interval preceding the Consent Date
	Previous failure of all three Primary AF Drugs (1° AFDs) for either effectiveness or intolerance
	Predicted need for use of any of the Primary AF Drugs (1° AFDs) or Secondary AF Drugs (2° AFDs) listed in Appendix One for "pill in pocket" therapy or any other use for any condition during the 12 month study follow-up period, other than for treatment of documented recurrent AF
	Any cardioversion (drug or electric) for AF during the 3 month interval preceding the Consent Date
	More than two cardioversions (drug or electric) for AF within the 2 years preceding the Consent Date
	Myocardial infarction, PCI / PTCA or coronary artery stenting during the 3 month interval preceding the Consent Date
	Unstable angina
	Any cardiac surgery during the 3 month interval preceding the Consent Date
	NYHA class III or IV congestive heart failure
	Left ventricular ejection fraction (LVEF) < 40% by TTE during the 3 month interval preceding the Consent Date
	2° (Type II) or 3° atrioventricular block
	Presence of a permanent pacemaker, biventricular pacemaker, atrial defibrillator or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
	Any cerebral ischemic event (strokes or TIAs) during the 6 month interval preceding the Consent Date.

2. Follow-up Schedule

For subjects randomized to the Experimental group, the Start Date was the day of the initial cryoablation procedure as outlined in the clinical protocol. After the cryoablation procedure and prior to hospital discharge, Experimental subjects underwent physical examination medication review, post-procedural inspiration/expiration chest x-ray (CSR), screening for adverse events, 12-lead ECG, National Institutes of Health Stroke Scale (NIHSS) screening establishment of systemic oral anticoagulation, institution of study AF Drug treatment, training and scheduling of TTM transmissions, a trans-thoracic echocardiogram and laboratory testing. For subjects randomized to the Control group, the Start Date was the day Study AF Drug was initiated.

All study subjects were subject to a 90 day Blanked Follow-up Period during which Experimental subjects could undergo a reablation procedure with cryoablation and the Control subjects could undergo AF Drug optimization. All study subjects were required to have follow-up assessments at 1, 3, 6, 9 and 12 months including history, physical examination, ECG, blood work, NIHSS screening, documentation of the use of Study AF Drugs and concomitant cardiovascular medication, occurrence of AF Interventions, and an adverse event review. The 9-month assessment was a telephone interview regarding arrhythmia recurrence, use of Study AF Drugs and concomitant cardiovascular medications, occurrence of AF Interventions and an adverse event review. Subjects were trained in the use of the transtelephonic monitoring and instructed to obtain and transmit a recording to the ECG Core Laboratory every week at a scheduled time and whenever symptomatic. At 6-and 12-months, 24-hour Holter monitoring was performed. A magnetic resonance imaging (MRI) or computerized tomography (CT) scan of the pulmonary veins was performed for all cryoablated subjects at baseline, 6 and 12 months after the first cryoablation procedures. Adverse events and complications were recorded at all visits.

Control subjects who demonstrated Chronic Treatment Failure and crossed over to cryoablation were maintained on dual follow-up schedules. The follow-up is summarized below in Table 5.

Table 5: Follow-up Schedule and Evalutations

Procedure [C = Control, E = Experimental]	Baseline	Randomization	Experimental Subjects only			1 month visit	3 month visit	6 month visit	9 month call	Unscheduled visit	12 month visit	Termination visit
			Procedure	Post-procedure	Discharge							
Consent [C, E]	X											
12 lead ECG [C, E]	X			X (1)	X (1)	X	X	X		X	X	X
History / P.E. [C, E]	X				X (1)	X	X	X	X(2)	X	X	X
CBC [C, E]	X				X (1)							
Creat, plts, PT, PTT [C, E]	X											
INR [C, E]	X				X (1)	X (3)	X (3)	X (3)		X (3)	X (3)	X (3)
TSH [C, E]	X											
HCG (4) [E]	X											
TTE [C, E]	X (5)			X (1, 6)								
TEE (1) [E]	X (1, 7)											
MRI or CT (1) [E]	X(1, 8)							X (1,9)			X (1,9)	X (1,9)
Medication review [C, E]	X				X (1)	X	X	X	X	X	X	X
24 hr Holter monitoring [C, E]	X (10)							X			X	X
CASI screen [C, E]	X										X	X
NIH Stroke Scale [C, E]	X				X (1)	X	X	X			X	X
SF-36 [C, E]	X										X	X
Chest X-ray [E]	X (1)				X (1)	X (1,12)	X (1,12)	X (1,12)			X (1,12)	X (1,12)
Study AFD [C, E]		Study subjects managed according to Standard Antiarrhythmic Treatment (SAT) procedures										
Cryoablation (1) [E]			X (1)									
AE review [C, E]			X (1)	X (1)	X (1)	X	X	X	X	X	X	X
TTM training [C, E]		X (C)			X (E)							

Procedure [C = Control, E = Experimental]	Baseline	Randomization	Experimental Subjects only			1 month visit	3 month visit	6 month visit	9 month call	Unscheduled visit	12 month visit	Termination visit
			Procedure	Post-procedure	Discharge							
TTM recording **[C, E]**						Study subjects managed according to TTM procedures (weekly and with Sx's)[11]						

Legend for Study Procedures Table:

(1) Experimental subjects only
(2) No PE at 9 month telephone follow-up
(3) If subject currently being treated with an anticoagulant
(4) Within 7 days prior to the procedure, female subjects only
(5) During the 3 month interval preceding the Consent Date
(6) Within 72 hours post procedure
(7) Within 3 days prior to the procedure
(8) During the 3 month interval preceding the Consent Date
(9) Follow-up PV imaging technology (MRI or CT) must be the same type as used for baseline
(10) During the 2 month interval preceding the Consent Date
(11) Each week on pre-specified day and whenever experiencing symptoms of tachyarrhythmia
(12) Only if post procedural chest X-ray demonstrated study-related phrenic nerve palsy, or if transient phrenic nerve block was observed during procedure

3. Clinical Endpoints

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

Cryoablation Procedure Events: (CPE) defined for ES only as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). See Table 6.

Table 6: Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE):	**With onset between Day 0 and:**
Access site complications requiring: Transfusion of 3 or more units or Surgical intervention or Permanent loss or functional impairment	Day 7
Cardiac damage (including MI)	Day 7
Pulmonary vein stenosis	12-month follow-up visit*
Atrio-esophageal fistula	12-month follow-up visit*
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

Major Atrial Fibrillation Events: (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. See Table 7.

Table 7: Major Atrial Fibrillation Event Categories

Major Atrial Fibrillation Events (MAFE):
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): AF recurrence or ablation Atrial flutter ablation (excluding Type I) Systemic embolization (not stroke) Congestive heart failure Hemorrhagic event (not stroke) Anti-arrhythmic drug: initiation, adjustment or complication*

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

Treatment Success: (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success and freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with $\alpha = 0.05$ and $\beta = 0.20$, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.

- Acute Procedural Success: (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only
- Chronic Treatment Failure: (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12-months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

4. Success/Failure Criteria

Experimental subject: Treatment Success is defined by the STOP AF clinical protocol as Acute Procedural Success AND no evidence of Chronic Treatment Failure.

Control subject: Treatment Success is defined by the STOP AF clinical protocol as no evidence of Chronic Treatment Failure.

5. Pre-Specified Statistical Plan

Analyses were performed according the Clinical Protocol (version 1.7), the Statistical Analysis Plan, and the supplemental document outlining the per protocol population. The Statistical Analysis Plan version 1.0 was reviewed and agreed upon with FDA and a supplement was created at the request of FDA outlining the Per Protocol Populations. Standard analytic methods were used throughout utilizing SAS, SPSS, Cytel, Statistica and NCSS software. Descriptive statistics were calculated for each quantitative and qualitative assessment. Shift tables were produced for select variables assessed at more than one time point. Sites were assessed for heterogeneity using Mantel-Haenszel test methods. The Student's t-test, Fisher's exact test, Cochran-Mantel-Haenszel test, ANOVA/ANCOVA using the PROC MIXED function in SAS and Kaplan-Meier analysis of survival using the log rank test were performed as required.

6. External Evaluation Groups

A Steering Committee was responsible for trial oversight, the protocol design, approval of both the Statistical Analysis plan and Clinical Study Report. In addition, an independent Clinical Events Committee (CEC) was responsible for the review and adjudication of major trial outcome data including a review of all adverse events and adjudication of all trial endpoints.

Two core laboratories were utilized for this clinical trial. The Imaging Core Laboratory was eImage which was responsible for reading pulmonary vein dimension from CT and MRI imaging utilizing blinded, independent assessment. The ECG Core Laboratory was Agility Research which was responsible for reading all of the study trans-telephonic monitoring transmissions and Holter monitors.

B. Accountability of PMA Cohort

At the time of database lock, of 258 patients enrolled in PMA study, 241 patients (93%) were available for analysis at the 12 month post-operative visit.

The first subject was enrolled on 10 October 2006. The first Experimental Subject was cryoablated on 16 October 2006, the first Control Subject began study-directed AF Drug therapy on 03 November 2006. The last original 12 month study follow-up visit took

place on 06 July 2009 and the last follow-up visit for subjects who were randomized to the Control group and crossed over to cryoablation was 06 May 2010.

Enrollment and accountability are summarized in the following table.

Table 8 Subjects Accountability and Disposition

Subject Disposition	Control Subjects	Experimental Subjects	All Subjects
Subjects provisionally enrolled and randomized	**87**	**171**	**258**
Screen Failures	1	5	6
Withdrawal of Consent	4	3	7
Subjects enrolled	**82**	**163**	**245**
Death	0	1	1
Lost to Follow-up	0	0	0
Withdrawal of Consent	3	0	3
Subjects completing 12 month follow-up	**79**	**162**	**241**
Control Subjects crossing over to cryoablation	**65**		
Experimental Subjects undergoing reablation		**31**	

Study populations for analysis were:

- Safety Population (n = 245): pre-specified, included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations:
  - Modified intent-to-treat (mITT) (n = 245): pre-specified modified intent-to-treat (mITT), included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations (114 ES, 67 CS);
- Cryoablated Control Population (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.

- Reablated Experimental Population (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow up schedule as determined by initial study cryoablation procedure.

C. Study Population Demographics and Baseline Parameters

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable, between the randomized groups, as summarized in Table 4 and Table 5

Study populations were comparable, as summarized in the following tables.

Table 9: Baseline Demographics – Age, Echocardiography, AF Symptoms, SF-36 Score

	All Subjects Mean (SE) N Median(Min, Max) N = 245	Control Subjects Mean (SE) N Median(Min, Max) N = 82	Experimental Subjects Mean (SE) N Median(Min, Max) N = 163	Difference [95% 95%CI]	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [-2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (28, 54)	40.3 (5.1) 163 40 (24, 50)	-0.7 [-2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	-0.7 [-2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [-7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.00 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [-4.3, 5.0%]	0.870

AP = Antero-posterior; EF = Ejection Fraction

Table 10: Baseline Demographics – Gender, Ethnicity and NYHA Class

		All Subjects % (n) N = 245	Control Subjects % (n) N = 82	Experimental Subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardio-vascular Risk Factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2%(118)	48.8% (40)	47.9% (78)	0.893

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

Summary of STOP AF subject demographics

The STOP AF Pivotal trial population achieved its intended target population of subjects with PAF and otherwise good cardiovascular health. Review of demographic and baseline data demonstrated that the Control and Experimental Subject groups were highly comparable, with no clinically significant differences in any parameter compared.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the full cohort of 163 patients who were enrolled, randomized, and received treatment. The key safety outcome for this study are presented below in Table 11 & Table 16. Adverse effects are reported in Table 12 to Table 20.

The primary safety outcomes, Cryoablation Procedure events (CPE) and Major Atrial Fibrillation Events, were both met.

STOP AF definitions

Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Adverse event resulting in death
- Adverse event which is life-threatening
- Adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Adverse event resulting in a persistent, significant disability or incapacity
- Adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

Cryoablation Procedure Events (CPEs), assessed only for ES for procedural safety, which were device or procedure related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy and death; and

Major Atrial Fibrillation Events (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP-AF study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% rate of CPE (UCB of 6.3%) compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of symptomatic pulmonary vein stenosis.

Table 11: Primary Safety Outcome: Cryoablation Procedure Events

Primary Safety Outcome: CPE	Experimental Subjects % (n / N)	95% Upper Confidence Bound	p value
Experimental Subjects with one or more CPE	3.1% (5 / 163)	6.3%	< 0.001

Table 12 lists the individual CPEs that were reported during the STOP AF trial.

Table 12: Experimental Subjects- Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects % (n) N = 163	95% One-Sided Upper Confidence Bound [1]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury [2]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis [3]	1.2% (2)	3.8%

[1] Based on Clopper-Pearson confidence intervals.

[2] Four (4) Experimental Subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. See Section 5.6.7 Transient Phrenic Nerve Dysfunction and Phrenic Nerve Palsy.

[3] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary vein stenosis: PV stenosis was defined by the study protocol as 75% reduction in calculated cross sectional area which is roughly a 50% decrease in diameter. The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (Table 8). Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE. Based on a multivariate analysis there were are no known contributing factors to the incidence of PV stenosis.

Table 13:: Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation [1] % (n) [95% CI] [2] N = 132	Two Cryoablations (n) [95% CI] [2] N = 31	Any Cryoablation % (n) [95% CI] [2] N = 163	One Cryoablation (n) [95% CI] [2] N = 65	Any Cryoablation (n) [95% CI] [2] N = 228
Stenosis in ≥ 1 PV at	2.3% (3)	6.5% (2)	3.1% (5)	3.1% (2)	3.1% (7)

6 or 12 Months [3]	[0.5, 6.5%]	[0.8, 21.4%]	[1.0, 7.0%]	[0.4, 10.7%]	[1.2, 6.2%]

[1] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.
[2] Clopper-Pearson confidence intervals.
[3] Each subject is counted only once within each time point.
CI = confidence interval; PV = pulmonary vein.

Phrenic Nerve Palsy: Twenty nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (Table 9). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Of 259 cryoablation procedures, 230 (88.8%) were not associated with PNP. Twenty five (25) (11%) were associated with PNP which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (Table 10). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

Table 14: Phrenic Nerve Palsy Procedures

Phrenic Nerve Palsy	**First Experimental Ablation Procedures % (n) [95% CI] N = 163 [1]**	**Experimental Reablation Procedures % (n) [95% CI] N = 31 [1]**	**Crossover Control Ablation Procedures % (n) [95% CI] N = 65 [1]**	**All Ablation Procedures % (n) [95% CI] N = 259 [1]**
Procedures free of PNP [2]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP [2]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[1] N = the total number of cryoablation procedures of this type.
[2] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second reablation procedure (both of which resolved).

Table 15: Phrenic Nerve Palsy Subjects

Phrenic Nerve Palsy	**First Experimental Ablation Subjects % (n) [95% CI] N = 163 [1]**	**Experimental Reablation Subjects % (n) [95% CI] N = 31 [1]**	**Crossover Control Ablation Subjects % (n) [95% CI] N = 65 [1]**	**All Ablated Subjects % (n) [95% CI] N = 228 [1]**
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28)[3] [8.3, 17.3%]

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163 [1]	Experimental Reablation Subjects % (n) [95% CI] N = 31 [1]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65 [1]	All Ablated Subjects % (n) [95% CI] N = 228 [1]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4)[3] [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25)[3] [7.2, 15.8%]

[1] N = the total number of subjects undergoing cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing non-inferiority for the MAFE free rate was set at 10%. ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference $\leq 10\%$).

Table 16: Primary Safety Outcome: Freedom from MAFE

Primary Safety Outcome: Freedom from MAFE	Control Subjects % (n / n) [95% CI]	Experimental Subjects % (n / n) [95% CI]	Difference [95% CI]	Test for Non-inferiority $\delta = 0.10$ p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [-1.1, 12.1%]	**< 0.001**

The observed categories of MAFEs are displayed for both treatment groups below.

Table 17: Subjects with One or More MAFEs by Category, Safety Population

MAFE Categories	Control Subjects % (n / N) [95% CI]	Experimental Subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	-5.4% [-12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	-6.5% [-11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	-5.5% [-10.8, -0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	-1.2% [-3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1/ 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	-1.2% [-5.0, 2.5%]	0.603
Anti-arrhythmic drug: initiation, adjustment or complication *	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	-4.3% [-9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1/ 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000

*Excludes control subject treatment initiation

There were no pre-specified secondary safety endpoints.

Additional Safety Information from the STOP AF Pivotal Trial

Serious Adverse Events

A total of 55 serious adverse events (SAE) in 32 study subjects were reported by Investigators during the first 12 months of study follow-up. Twenty two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 18: Subjects with One or More Serious Adverse Events, Safety Population

Serious Adverse Events	Control Subjects % (n / n)	Experimental Subjects % (n / n)	Difference [95% CI]	p value
Serious Adverse Events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [-11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables.

Table 19: Serious Adverse Events Occurring in Control Subjects, Safety Population

Control Subject	Verbatim	DR	PR	MAFE	Outcome
R0209	Worsening of AF	No	No	**Yes**	Recovered
R0331	Gastrointestinal bleeding	No	No	**Yes**	Recovered
R0404	Atrial fibrillation	No	No	**Yes**	Recovered
R0626	Appendicitis	No	No	No	Recovered
R0808	Right diaphragm paresis	**Yes**	No	No	Recovered
R1003	Non bacterial meningitis	No	No	No	Recovered
R1004	Increasing persistent A fib	No	No	**Yes**	Recovered
R1008	A fib persistent-drug load	No	No	**Yes**	Recovered
	Recurrent atrial fibrillation	No	No	**Yes**	Recovered
	Pericardial effusion	No	No	No	Recovered
	Cardiopulmonary arrest with resuscitation	No	No	No	Sequelae
	Cardiac tamponade	No	No	No	Recovered
	Subdural hematoma from fall	No	No	**Yes**	Sequelae
	Altered mental status S/P cardiac arrest	No	No	No	Recovered
	Acute renal failure requiring dialysis	No	No	No	Recovered
	Persistent atrial fibrillation	No	No	**Yes**	Recovered
R1108	Worsening atrial flutter	No	No	**Yes**	Recovered
	Worsening flutter	**Yes**	No	**Yes**	Recovered
	Atrial flutter-recurrent	No	No	**Yes**	Recovered
R2006	Left atrial appendage thrombus	No	No	No	Recovered
R2102	Rapid atrial flutter	No	No	**Yes**	Recovered
R2505	Right wrist heparin lock insertion site infection	No	No	No	Recovered

DR = device-related, PR = procedure-related, assessed as "Yes" for "definitely related" or "likely related."

Control Subjects were not assessed for Cryoablation Procedure Events (CPE) in relation to crossover cryoablation procedures, as stipulated in the protocol.

MAFE = Major Atrial Fibrillation Event, AF, A fib = atrial fibrillation, S/P = status post, NA = not applicable, Sequelae = Recovered with sequelae.

Table 20: Serious Adverse Events Occurring in Experimental Subjects, Safety Population

Exp'l Subject	Verbatim	DR	PR	CPE	MAFE	Outcome
R0202	Worsening AF	No	No	No	No	Recovered
R0328	Myocardial infarction	No	No	No	**Yes**	Fatal
	Multiple organ failure	No	No	No	**Yes**	Fatal
R0519	Interstitial pneumonitis	No	No	No	No	Recovered
R0606	Pericardial effusion (tamponade)	No	**Yes**	**Yes**	No	Recovered
R0702	Acute pyelonephritis 2° to vesical catheter	No	**Yes**	No	No	Recovered
R0715	Occlusion left inferior pulmonary vein	**Yes**	NA	**Yes**	No	Sequelae
R0903	Hematoma from left groin	No	**Yes**	No	No	Recovered
R0907	Cardiopulmonary decompensation-etiology uncertain	No	**Yes**	No	**Yes**	Recovered
	Deep vein thrombosis	No	No	No	No	Recovered
	Physical deconditioning 2° to procedural complications and immobilization	No	No	No	No	Recovered
	Worsening A fib	No	No	No	No	Recovered
	Pneumonia	No	**Yes**	No	No	Recovered
	Recurrent rapid A fibrillation	No	**Yes**	No	No	Recovered
R1002	Pneumonia	No	No	No	No	Recovered
R1007	Ileitis	No	No	No	No	Recovered
	Focal hemorrhage of ileum 2° to warfarin induced coagulopathy	No	No	No	**Yes**	Recovered
R1014	Escherichia coli bacteremia	No	**Yes**	No	No	Recovered
R1103	Left upper + lower pulmonary vein stenosis	**Yes**	No	**Yes**	No	Ongoing
R1109	Non Q wave myocardial infarction	No	**Yes**	**Yes**	No	Recovered
R1113	Worsening atrial flutter	No	**Yes**	**Yes**	No	Recovered
R1301	Pneumonia left lower lobe	No	**Yes**	No	No	Recovered
R1404	Right lung blebs with persistent air leak	No	No	No	No	Sequelae
R2005	Wegener's granulomatosis	No	No	No	**Yes**	Sequelae
	Worsened AF with rapid ventricular response	No	No	No	**Yes**	Recovered
	Pulmonary embolus	No	No	No	No	Recovered

Table 20: Serious Adverse Events Occurring in Experimental Subjects, Safety Population						
Exp'l Subject	Verbatim	DR	PR	CPE	MAFE	Outcome
	Abdominal wall hemorrhage	No	No	No	**Yes**	Recovered
	Pneumonia	No	No	No	No	Recovered
	Left popliteal deep vein thrombosis	No	No	No	No	Recovered
	Sepsis induced hypotension	No	No	No	No	Recovered
R2101	Subarachnoid hemorrhage	No	No	No	**Yes**	Recovered
R2103	Worsening atrial fib-flutter	No	NK	No	No	Recovered
R2503	Acute exacerbation of asthma	No	No	No	No	Recovered

DR = device-related, PR = procedure-related, assessed as "Yes" for "definitely related" or "likely related."

CPE = Cryoablation Procedure Event. MAFE = Major Atrial Fibrillation Event, AF, A fib = atrial fibrillation, S/P = status post, Unk = unknown relatedness, Sequelae = Recovered with sequelae.

Death Summary

No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

Pulmonary Vein Stenosis

Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement.

Phrenic Nerve Injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days (range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 month visit.

Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as "whites spots in both eyes" and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

Vascular Access Complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

Summary of STOP AF Pivotal Trial Adverse Events as Categorized Using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6 CS and 4 ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one procedure-related AE. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects, 9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control: 12.3%; Experimental: 18.4%), Nervous System Disorders (Control: 13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28 subjects, 12.3%).

Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

2. Effectiveness Results

The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, $p < 0.001$) and was, therefore, met.

The STOP AF Protocol defined three (3) Primary Effectiveness Outcome Measures:

- Acute Procedural Success (APS), the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- Chronic Treatment Failure (CTF), defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- Treatment Success (TS), defined as:
  - Experimental Subjects: Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - Control Subjects: Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES (Table 17). Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block.

Table 17 Experimental First Procedures: Acute Pulmonary Vein Isolation Rates

Vein(s)	Proportion Isolated % (n / N)
≥ 3 PVs (APS)	98.2% (160 / 163)
RSPV	98.1% (159 / 162)
RIPV	97.4% (152 / 156)
LSPV	96.7% (146 / 151)
LIPV	97.4% (149 / 153)

APS = Acute Procedural Success

PV – pulmonary vein, R = right, L = left, I = inferior, S = superior.

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, $p < 0.001$) (see Figure 1 and Table 18)

Figure 1: Kaplan Meier Display of Continued Treatment Success by Group Through 12 Months, Modified Intent to Treat Population

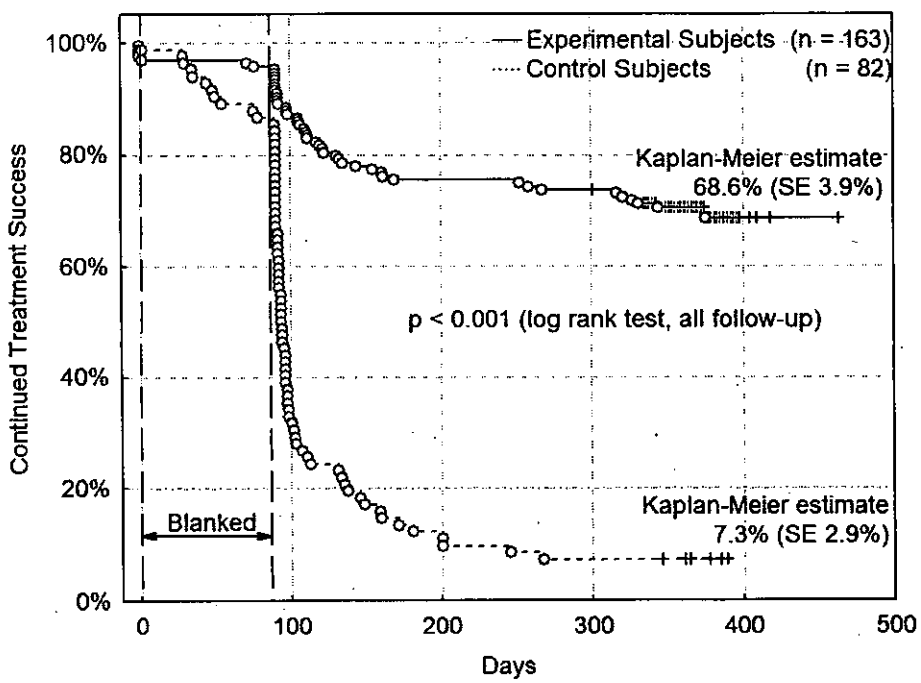


Table 18 Primary Effectiveness Outcome: Treatment Success (mITT Population)

Primary Effectiveness Outcome	Control Subjects % (n / N) [95% CI]	Experimental Subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment Success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	< 0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- AF Drug Free Treatment Success: Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.

  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow up period (Table 19).

Table 19: Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [1] [95% CI] N = 82	Experimental Subjects % (n / N) [1] [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs [2]	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

[1] Clopper-Pearson confidence intervals

[2] Treatment Success at 12 months includes all enrolled subjects grouped by AF Drug use during Non-Blanked Follow-up Period. The study protocol stipulated that AF Drugs in Experimental Subjects were to be stopped by the 3 month follow-up visit (90 ± 14 days)

- Reduced Use of AF Drugs: 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- Reduced Use of warfarin: 76% of all ES were off warfarin during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from warfarin use during the last 3 months of follow-up. The Arctic Front Cardiac CryoAblation Catheter was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.
- Improved Quality of Life: ES showed improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- Reduced Symptoms: ES had a significant reduction in AF symptomatic burden after cryoablation.
- Equally Effective in Early Persistent AF: Of the 37 ES who had a history of cardioversion for AF prior to enrollment, 30 (81.1%) had Treatment Success.
- Effectiveness by Balloon Size: Treatment success was 70% among cryoablations with balloon size 23mm, 63.3% among cryoablations with balloon size 28mm, and 76.2% among subjects with both balloon sizes utilized (Table 20).

Table 20: Primary Effectiveness Outcome; Proportion of ES with Treatment Success at the 12 Month Follow Up Visit

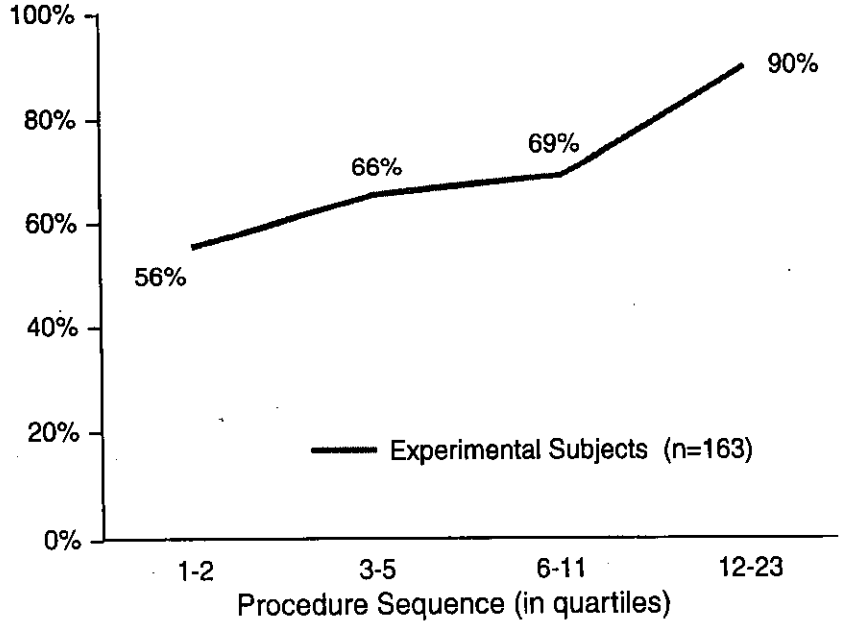
Cohort	Experimental Subjects % (n / N) [1] [95% CI] [2] N = 163
Treatment Success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

[1] The primary effectiveness outcome of Treatment Success at 12 months includes all enrolled and randomized subjects.

[2] Clopper-Pearson method for estimating exact binomial confidence intervals.

- Effectiveness by number of procedures performed: A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. Figure 1 illustrates that treatment success improved as the number of procedures performed increased at a given site.

Figure 1: Procedure Frequency and Treatment Success



Atrial Flutter Outcomes:

- Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) with Freezor® MAX Cryocatheter was performed in 66 ES. Bi-directional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

3. Subgroup Analyses

STOP AF had no prospectively defined subgroup evaluations planned.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. CAP-AF Continued Access Continued Access Protocol (PS-024)

Medtronic Cryocath LP plans to commercialize a version of the Arctic Front® Cryocatheter System [Arctic Front® Cardiac CryoAblation Catheter Models 2AF232 / 2AF282 and CryoConsole Model 106A2] that incorporates minor design modifications from the version that was evaluated in the STOP AF Pivotal Trial [Arctic Front® Cardiac CryoAblation Catheter Model 2AF230 / 2AF280 and CryoConsole Gen V]. The Continued Access Protocol (CAP AF) was designed to provide continued access to the investigational devices for participating Investigators as well as provide scientific evidence regarding the acute safety and effectiveness of the modified Arctic Front® Cardiac CryoAblation Catheter System with the adjunctive use of the Freezor® *MAX* Cardiac CryoAblation Catheter in patients with PAF. This study was a non-randomized controlled study of patients with paroxysmal atrial fibrillation (PAF) who had been referred for ablative intervention after failing one or more anti-arrhythmic drugs used in the treatment of AF.

i. Summary of Results

Overview: Sixty-nine (69) subjects were enrolled to date in this nonrandomized continued access protocol of balloon cryoablation for the treatment of paroxysmal atrial fibrillation at eight (8) US investigational centers. Three (3) subject screen-failed, one (1) withdrew and sixty-five (65) were treated under this protocol. No subjects were lost to follow-up and four (4) subjects have so far completed the 12 month follow-up. Sixty-four (64) subjects were treated with the Arctic Front® CryoAblation System and one (1) case was performed using radiofrequency energy due to inability to gain left atrial access with the cryocatheters. Right CTI ablation for Flutter using Freezor® *MAX* was performed in sixteen (16) subjects and radiofrequency energy was also used in one (1) subject.

Investigational devices: Following the STOP AF Pivotal IDE Study, modifications were made to the investigational devices. Approval to study the modified devices in this Continued Access

Protocol was granted by FDA. The primary modification to the Arctic Front® Cryoablation System related to operator ease of use as well as manufacturability.

Ablation Procedures: Sixty-four (64) subjects underwent initial cryoablation procedures, and four (4) subjects were reablated. Procedure length averaged 317 minutes, with 129 minutes of cryocatheter insertion time and 45 minutes of fluoroscopy. Pulmonary vein isolation was achieved with 2 to 4 cryoapplications per vein. Flutter line cryoablation at the right cavo-tricuspid isthmus was performed in sixteen (16) subjects using the Freezor® *MAX* cryocatheter and in one (1) subject with radiofrequency device. These ablation parameters compared favorably with the Pivotal IDE study data.

Effectiveness Outcomes: Acute Procedural Success (Primary Effectiveness) was 96.9%. Acute Vein Success (electrical isolation of a vein at the conclusion of the procedure) was achieved in 94.7% of pulmonary veins attempted. These high acute success rates are consistent with previous trials of this device system. The proportion of subjects that have met the criteria of acute procedural success and freedom from chronic treatment failure is 50/65 (76.9%) subjects. In addition, no new device functionality issues were reported with procedural device functionality issues occurring in 26.6% of cases.

Safety Profile: There were 150 adverse events in 75.4% of treated subjects. There were no deaths and the majority of AEs were mild and resolved completely. Among the adjudicated events, there was one (1) Cryoablation Procedure Event. Also, 61/65 subjects were free of Major Atrial Fibrillation Events (MAFEs) (93.8%). The current rate of post-procedure phrenic nerve palsy of 4.3% is lower than that observed during the STOP AF pivotal IDE study (11.2%).

Assessment of pulmonary vein dimensions via independent Core Lab analysis showed that none of the 23 subjects had pulmonary vein stenosis at 12 months.

Conclusion: These results support the acute effectiveness and safety of the Arctic Front® CryoAblation System in the treatment of subjects with paroxysmal atrial fibrillation. The technology demonstrated 96.9% acute procedural success and an acceptable safety profile.

Comparison of Selected Clinical Outcomes: STOP AF and CAP AF

Analyses were performed to assist in the comparison of the Acute Procedural Success, 30 day safety outcomes and other safety measures assessed in the STOP AF Pivotal Study (PS-023) and the CAP-AF Continued Access Protocol (PS-024).

Summary of Analyses

Acute Procedural Success (APS): APS analyses utilized the STOP AF Experimental Subjects from STOP AF (n = 163). The CAP AF APS dataset included 67 CAP AF Interim Subjects with confirmed, available data from the procedure. The results suggest that the Acute Procedural

Success rates in these two studies are comparable, with an APS rate of 98.2% in the STOP AF cohort and 95.5% in the CAP AF cohort (difference -2.6%, p = 0.36).

Table 25 Acute Procedural Success Rate, Modified Intent-To-Treat Population

	STOP AF Experimental Subjects % (n / N) [95% CI] [1]	CAP AF Interim Subjects % (n / N) [95% CI] [1]	Difference [95% CI] [2]	p value [3]
Acute Procedural Success	98.2% (160 / 163) [94.7, 99.6%]	95.5% (64/67) [87.5, 99.1%]	-2.6% [-16.8,11.6%]	0.36

[1] Exact binomial confidence intervals.

[2] Difference and confidence interval of difference by method of Farrington and Manning.

[3] Fisher's Exact Test.

Thirty-Day Safety Outcomes: The safety comparisons utilized the STOP AF adverse event listing for all adverse events occurring with an onset date between Day 0 and Day 30, inclusive, in the STOP AF Experimental Subjects, as this was the most relevant population for comparison.

All 67 CAP AF Interim Subjects with one or more post-ablation CRF available were considered on an intent-to-treat basis, noting that 5 of 67 had no 1 month CRF data available as of May 5, 2010. Of these 5 subjects, 3 (CAP-307, CAP-906 and CAP-907) had one or more qualifying adverse events in the listing.

The following categories of events were compared for both STOP AF Experimental Subjects and CAP AF Interim Subjects.

- All adverse events (onset Day 0 – 30), including
  - device-related adverse events
  - procedure-related adverse events
- Serious adverse events (SAEs) (onset Day 0 – 30), including
  - device-related adverse events
  - procedure-related adverse events
- Cryoablation Procedure Events (CPEs) with onset between Day 0 and 30
- Major Atrial Fibrillation Events (MAFEs) with onset between Day 0 and 30

These analyses showed significantly lower proportions of CAP AF Interim Subjects were found to have one or more adverse events as of the interim analysis date, including device- and procedure-related adverse events, compared with STOP AF Experimental Subjects. No claim of improved safety is warranted based on this interim finding, but it does suggest that the CAP AF performance is not worse and may simply reflect incomplete follow-up and / or greater operator

experience at these sites given their prior participation in STOP AF. There were no significant differences in SAE proportions between the two populations of subjects, nor in the proportions of subjects with CPEs or MAFEs with onset between Days 0 – 30.

Table 26 **Proportion of Subjects with One or More Adverse Events from 0 – 30 Days, Safety Population**

Categories of Adverse Events with Onset Days 0 – 30	STOP AF Experimental Subjects % (n / N) [95% CI] [1]	CAP AF Interim Subjects % (n / N) [95% CI] [1, 2]	Difference [95% CI] [3]	p value [4]
All AEs	93.9% (153 / 163) [89.0, 97.0%]	67.2% (45 / 67) [54.6, 78.2%]	-26.7% [-38.5, -14.9%]	<0.001
Device-related AEs	40.5% (66 / 163) [32.9, 48.4%]	25.4% (17 / 67) [15.5, 37.5%]	-15.1% [-28.0, -2.3%]	0.03
Procedure-related AEs	71.2% (116 / 163) [63.6, 78.0%]	55.2% (37 / 67) [42.6, 67.4%]	-15.9% [-29.7, -2.2%]	0.02
All SAEs	6.1% (10 / 163) [3.0, 11.0%]	3.0% (2 / 67) [0.4, 10.4%]	-3.2% [-8.6, 2.3%]	0.52
Device-related SAEs	0.0% (0 / 163) [0.0, 2.2%]	0.0% (0 / 67) [0.0, 5.4%]	0.0%	NA
Procedure-related SAEs	3.1% (5 / 163) [1.0, 7.0%]	3.0% (2 / 67) [0.4, 10.4%]	-0.1% [-4.9, 4.8%]	1.00
CPEs ≤ Day 30 [5]	1.2% (2 / 163) [0.1, 4.4%]	1.5% (1 / 67) [0.04, 8.0%]	0.3% [-3.1, 3.6%]	1.00
MAFEs ≤ Day 30 [5]	0.0% (0 / 163) [0.0, 2.2%]	0.0% (0 / 67) [0.0, 5.4%]	0.0%	NA

[1] Exact binomial confidence intervals.

[2] Interim Subject data from CAP AF not yet formally adjudicated by Clinical Events Committee.

[3] Difference and confidence interval of difference by method of Farrington and Manning.

[4] Fisher's Exact Test.

[5] CPE and MAFE status for all CAP AF adverse events are provisional determinations by Medical Monitor based on trial definitions and adjudication procedures utilized in STOP AF.

Review of the types of SAEs reveal that both STOP AF Experimental Subjects and CAP AF Interim Subjects had urinary tract infections related to the procedure and post ablation atrial arrhythmias, expected complications for interventional electrophysiology procedures. See Table 27 and Table 28

Table 27 **SAEs with Onset During Days 0 – 30 in STOP AF Experimental Subjects**

STOP AF SubjID	Verbatim	DR	PR	CPE	MAF E	Outcome
R0202	Worsening AF	No	No	No	No	Recovered
R0519	Interstitial pneumonitis	No	No	No	No	Recovered

STOP AF SubjID	Verbatim	DR	PR	CPE	MAF E	Outcome
R0606	Pericardic effusion (tamponade)	No	Yes	Yes	No	Recovered
R0702	Acute pyelonephritis 2° to vesical catheter	No	Yes	No	No	Recovered
R0903	Hematoma from left groin	No	Yes	No	No	Recovered
R0907	Worsening A fib	No	No	No	No	Recovered
R1014	Escherichia coli bacteremia	No	Yes	No	No	Recovered
R1109	Non Q wave myocardial infarction	No	Yes	Yes	No	Recovered
R1301	Pneumonia left lower lobe	No	No	No	No	Recovered
R2503	Acute exacerbation of asthma	No	No	No	No	Recovered

DR = device-related, PR = procedure-related, assessed as "Yes" for "definitely related" or "likely related."

CPE = Cryoablation Procedure Event. MAFE = Major Atrial Fibrillation Event, AF, A fib = atrial fibrillation, Sequelae = Recovered with sequelae.

Table 28 SAEs with Onset During Days 0 – 30 in CAP AF Interim Subjects

CAP AF SubjID	[Provisional Diagnosis] Verbatim	DR	PR	CPE[1]	MAFE[1]	Outcome
CAP 1202	[Infection] Urinary symptoms. Pain & chills. Diagnosed test for infection, hospital admission and treated with antibiotics - ? D/C 9/26/09	No	Yes	No	No	Recovered
CAP 1205	[Atrial Flutter] Admitted to SHC in atrial flutter on 9/14/09, treated with diltiazem drip, ? Anticoagulant. Discharged 9/18/09	No	Yes	Yes	No	Recovered

[1] CPE and MAFE status for all CAP AF adverse events are provisional determinations by Medical Monitor based on trial definitions and adjudication procedures utilized in STOP AF.

DR = device-related, PR = procedure-related, assessed as "Yes" for "definitely related" or "likely related."

CPE = Cryoablation Procedure Event. MAFE = Major Atrial Fibrillation Event.

Other Adverse Events of Interest: All STOP AF Experimental Subjects completed 12 month follow-up for safety for 163 subjects (excluding 1 death at 10½ months). CAP AF Interim Subjects have a mean follow-up of 4.85 months (median 5.72, range 0.03 – 11.37 months) as of the May 5, 2010 cutoff date. Thus, a comparison of these two populations for adverse events with longer time frames carries an inevitable bias in favor of CAP AF Interim Subjects whose exposure after Day 30 is incomplete.

Nonetheless, assessment of additional safety outcomes of interest was made, although no differences or p values were calculated. CAP-AF Interim procedures had a 5.6% rate of phrenic nerve palsy compared with a rate of 11.2% for STOP AF procedures. Neither subject group had any atrio-esophageal fistulae. Post-cryoablation pulmonary vein imaging has been performed on 23 CAP AF Interim Subjects and zero (0) have been diagnosed with pulmonary vein stenosis.

Table 29 Additional Safety Outcomes, Safety Population

Categories of Adverse Events	STOP AF All Ablation Procedures % (n / N) [95% CI] [1]	CAP AF Interim Procedures % (n / N) [95% CI] [1, 2]
Phrenic nerve palsy	11.2% (29/259) [7.6, 15.7%]	5.6% (4 / 71) [1.6, 13.8%]
Atrio-esophageal fistula	0.0% (0 / 163) [0.0, 2.2%]	0.0% (0 / 67) [0.0, 9.0%]

[1] Exact binomial confidence intervals.

[2] Interim Subject data from CAP AF not yet formally adjudicated by Clinical Events Committee.

This comparison of selected outcomes from STOP AF and CAP AF allows a reliable conclusion that Acute Procedural Success rates were essentially identical, and that the safety outcomes assessed from Days 0 – 30 assessed in this report were not worse in CAP AF Interim Subjects when compared with STOP AF Experimental Subjects.

These analyses support Medtronic Cryocath's plans to commercialize the version of the Arctic Front® Cryocatheter System [Arctic Front® Cardiac CryoAblation Catheter Models 2AF232 / 2AF282 and CryoConsole Model 106A2] studied in the CAP AF Continued Access Protocol (CAP AF) that incorporates minor design modifications from the version that was evaluated in the STOP AF Pivotal Trial [Arctic Front® Cardiac CryoAblation Catheter Model 2AF230 / 2AF280 and CryoConsole Gen V].

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The safety results of the clinical studies indicate that the device is safe for the intended use.

B. Effectiveness Conclusions

The effectiveness outcomes of the clinical studies demonstrate that the device treatment is at least as effective as the study anti-arrhythmic drug therapy for the treatment of symptomatic paroxysmal atrial fibrillation at 12 months post-procedure.

C. Overall Conclusions

Pre-clinical testing of the Arctic Front® Cardiac CryoAblation Catheter and CryoConsole included verification and validation testing (device level, system level, and software), biocompatibility of patient-contacting materials; sterilization, packaging and shelf life testing, and animal studies. The results of this testing results confirmed that the Arctic Front® Cardiac CryoAblation Catheter and CryoConsole met the product specifications and its design is suitable for the intended use of the device.

The results of a pivotal, randomized (2:1), multi-center, clinical trial in 245 subjects (163 Experimental and 82 Control) with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation Drugs provided valid scientific evidence in support of safety and effectiveness of the devices. Acute Procedure Success (APS) was achieved in 98.2% (160/163) of Experimental Subjects. At 12 months, the proportion of Experimental Subjects with Treatment Success was 69.9%, while the proportion of Control Subjects with Treatment Success was 7.3%, yielding an absolute difference of 62.6%, which was statistically significant ($p < 0.001$, Fisher's Exact Test). Therefore, the primary effectiveness outcome was met. In the Experimental group, 74% were not on AF Drugs at 12 months. Both primary safety outcomes were met. Experimental Subjects had a 3.1% rate of Cryoablation Procedure Events (CPE) with an UCB of 6.3% which was significantly less than the pre-specified UCB of 14.8% ($p < 0.001$). Experimental Subjects had a 96.9% Freedom from Major Atrial Fibrillation Events (MAFE) rate, compared to Control Subjects who had a 91.5% rate ($p < 0.0001$, non-inferiority).

A comparison of acute procedure success and 30-day safety outcomes from a continued access study of the commercial version of the device showed equivalent performance to the device that was evaluated in the pivotal clinical trial.

In conclusion, the data in this application support the reasonable assurance of safety and effectiveness of the devices when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on December 17, 2010.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.